Localization and Surgical Treatment of Occult Insulinomas

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Management of patients with biochemical evidence of insulinoma and negative preoperative imaging studies (occult) tumors is controversial, varying from primarily medical management to aggressive, blind nearly total pancreatectomy to extirpate the tumor. Since 1982, 12 consecutive patients with occult insulinoma underwent preoperative portal venous sampling (PVS) for insulin followed by surgical exploration with intraoperative ultrasound (IOUS). Eleven of twelve patients (92%) had insulinoma removed and were cured. Portal venous sampling correctly predicted the location of the insulinoma in 9 patients (75%) and that no tumor would be found in another patient. A fourfold insulin gradient in the pancreatic tail of one patient correctly predicted that a distal pancreatectomy would remove the insulinoma despite the fact that neither palpation nor IOUS identified any tumor. Intraoperative ultrasound was the single best method to identify occult tumors because it correctly identified 10 of 11 insulinomas that were found, including five pancreatic head tumors that were not palpable. Palpation identified five insulinomas. Of the 10 tumors that were identified during operation by palpation or ultrasound, IOUS identified significantly more (100% *versus* 50%, p = 0.03) and guided the successful enucleation of each. The results support the strategy of preoperative PVS and operation with IOUS to localize and remove insulinoma in patients with occult tumors. Most tumors (75%) will be correctly localized to a specific pancreatic region by preoperative PVS and identified by IOUS (83%), allowing simple enucleation and biochemical correction of hypoglycemia. Morbid blind pancreatic resections are no longer indicated and long-term medical management of hypoglycemia should be reserved for the occasional patient (8%) who fails preoperative PVS and operation guided by IOUS.

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INSULINOMAS ARE THE most common islet cell tumor.[1] Because of their small size, they pose a major challenge in localization. If one excludes patients with Multiple Endocrine Neoplasia type 1, which includes only 5% of all patients with insulinomas,[2] insulinomas generally are benign (90%), intrapancreatic (nearly 100%), and solitary small neoplasms (measuring less than 2 cm).[3] Surgical enucleation or resection of insulinomas always has been the treatment of choice, and if achieved, results in cure of the hypoglycemia.[4] The major problem with insulinomas is accurate localization. When tumors are not localized, 'blind' distal, subtotal, nearly total, and/or total, pancreatectomies that also require concomitant splenectomy are recommended by many surgeons.[5-9] However these procedures are complicated by short-term morbidity (pancreatitis, pancreatic fistula, pancreatic abscess) and long-term morbidity (exocrine pancreatic insufficiency and diabetes mellitus).[5,6] The morbidity of major blind pancreatic resection, the reduced likelihood of finding the insulinoma in patients with occult tumors, and the benign nature of occult insulinomas has led some physicians to recommend medical management of the hypoglycemia with diet, diazoxide, and octreotide, and to withhold surgery unless patients are poorly controlled on medication or a tumor is identified clearly.[10] The best treatment results are obtained in patients who have accurate preoperative localization.

The diagnostic localization procedure of choice for insulinomas is selective angiography. In our experience[11] and the experience of others,[12] selective angiography has identified approximately 80% of insulinomas. However recent results indicate that fewer insulinomas are visualized accurately by angiography[13] and the incidence of patients with biochemical evidence of insulinoma and negative angiograms may be as high as 50%.[13] Other radiographic methods such as infusion computed tomography

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(CT), standard CT, ultrasound, and magnetic resonance imaging have been ineffective at localizing islet cell tumors, including these occult tumors.[10–14] If the incidence of patients with angiographically occult insulinomas is increasing, as it appears to be, then the role of surgery in the management of these patients is increasingly unclear.

In 1982, when we first began this study, two techniques were introduced that we thought might be helpful to localize occult insulinomas. Portal venous sampling (PVS) was reported and appeared promising.[15] Its potential to localize occult insulinoma had been speculated.[16] Intraoperative ultrasound (IOUS) was described[17] but its utility in localizing occult insulinomas had not been evaluated. In addition, because insulinomas are uniformly distributed throughout the entire pancreas,[18] perhaps PVS could indicate a pancreatic region on which to focus the IOUS. One of the early patients had dramatic results.[19] Portal venous sampling localized an insulinoma to the pancreatic head. At exploration the tumor was not palpable. Instead of requiring a Whipple pancreaticoduodenectomy, IOUS imaged a 8-mm insulinoma and guided the successful enucleation of it.[19] Therefore we began a prospective study to evaluate the ability of IOUS coupled with PVS sampling to localize and resect insulinomas in patients with occult insulinomas. We report here our results in 12 consecutive patients with occult insulinoma; that is, insulinomas not visualized before operation by any radiographic imaging study. The results demonstrate a remarkable degree of success at finding insulinomas in patients with occult tumors and suggest that intraoperative ultrasound is primarily responsible for the success.

Methods

Between July 1982 and January 1990, 23 patients with a diagnosis of insulinoma and without Multiple Endocrine Neoplasia Type I were eligible for the current study. Each patient had the diagnosis of insulinoma established by an inappropriate elevation of serum insulin level and hypoglycemia following a fast.[3] Factitious hypoglycemia was dismissed, as described previously.[20] Each patient had preoperative radiographic imaging studies, including ultrasound,[21] CT,[11] and selective pancreatic angiography.[11] Patients who had insulinomas visualized by any of these modalities (n = 11) were excluded from this study.

Twelve patients had no insulinoma localized (occult tumors) and compose the population of this study. Each patient underwent percutaneous transhepatic portal venous sampling with selective vein sampling for insulin concentrations, as described previously.[16] The insulin gradient, expressed as a percentage of the simultaneous peripheral sample, was calculated as follows: insulin gradient = 100 × [(maximal selective insulin concentration − simultaneous peripheral insulin concentration/(simultaneous peripheral insulin concentration)].[22] An insulin gradient of 50% or more was interpreted as localizing the insulinoma regionally to the head, body, or tail of the pancreas. Between 20 and 30 samples for insulin concentration were obtained from each patient with a median number of samples of 26.

Patients then underwent a trial of medical management of the hypoglycemia with frequent feedings and oral diazoxide to determine if, in the event of inability to operatively localize an insulinoma, medical management of hypoglycemia would be adequate.

All operations were performed in a similar manner. The head of the pancreas was exposed by performing an extended Kocher maneuver and the body and tail were exposed by entering the lesser sac and dividing along the inferior border of the pancreas. Systematic palpation of the entire pancreas was performed, followed by intraoperative real-time high-resolution ultrasound, as previously described.[23] Initially detailed palpation of the entire pancreas was performed and any identified abnormality was recorded. Then IOUS was performed and any abnormality identified was recorded. All abnormalities identified by palpation or IOUS were biopsied. Generally insulinomas were enucleated. Occult tumors in the pancreatic head were enucleated. Occult tumors in the body or tail were enucleated, unless they were adjacent to the pancreatic duct, in which case they were resected by a distal pancreatectomy. Blind resections of the pancreas were not performed. If an insulinoma could not be identified by intraoperative maneuvers, a pancreatic resection was performed only if an insulin gradient suggested a region to resect. Operative monitoring of blood sugar was not used as an indication to terminate the procedure and surgery was terminated if the pathologist diagnosed an islet cell tumor on frozen section or if the operation was thought to be futile.

Results of selective venous sampling, palpation, and operative ultrasound were compared to the final surgical pathologic result, as described previously.[23] Each patient was re-evaluated at least 3 months after surgery. Criteria for 'cure' (biochemical remission) of insulinoma include (1) no symptoms of hypoglycemia following a fast, (2) fasting blood glucose level more than 2.2 mmol/L (millimolar), (3) fasting serum insulin level less than 6 μU/mL, and (4) documented weight loss. Statistical comparison of proportions was performed by Fisher's exact test.

Results

Operative Tumor Localization

Eleven of twelve patients (92%) with occult insulinoma had tumors removed (Table 1). Each insulinoma was located within the pancreas. The mean diameter of these occult tumors was 1.2 cm (range, 0.7 to 2.5 cm) and the

TABLE 1. *Portal Venous Sampling and Operative Localization Maneuvers for Insulinoma Patients with Negative Preoperative Imaging*

Patient	Sex	Age (yrs)	Preoperative PVS* Site and Magnitude of Positive Insulin Gradient	Intraoperative† Palpation	Intraoperative† IOUS	Pathology Tumor Size and Location	Postoperative Outcome‡
1	F	29	Pancreatic tail 5150%	−	+	0.7-cm head	Cured
2	F	30	Pancreatic tail 225%	+	+	1.0-cm tail	Cured
3	F	31	Pancretic body 1358%	+	+	1.2-cm body	Cured
4	M	24	None	−	−	Not found	Not cured
5	F	54	Pancreatic tail 1348%	+	+	1.5-cm tail	Cured
6	F	30	Pancreatic tail 725%	+	+	2.5-cm tail	Cured
7§	M	34	Pancreatic tail 445%	−	−	1.0-cm tail	Cured
8	F	29	None	+	+	1.5-cm body	Cured
9	F	25	Pancreatic head 1251%	−	+	0.8-cm head	Cured
10‖	F	55	Pancreatic head 500%	−	+	1.0-cm head	Cured
11	F	34	None	−	+	0.8-cm head	Cured
12	F	25	Pancreatic head 740%	−	+	1.2-cm head	Cured

* Results of preoperative PVS for insulin were considered positive if the gradient was ≥50%.

† Intraoperative results were classified as (+) if a histologically proved insulinoma was identified or (−) if none was found.

‡ Patients were classified as cured or not cured as defined in Methods.

§ In patient #7, tumor was found by a distal pancreatectomy based on an insulin gradient in the pancreatic tail.

‖ Patient #10 previously had undergone an unsuccessful subtotal pancreatectomy.

tumors were distributed throughout the pancreas. None of the insulinomas had any pathologic features of malignancy. No patient had more than one tumor identified.

Ten patients had insulinoma accurately localized during operation, thus allowing enucleation. Five of the ten islet cell tumors found at surgery were localized by palpation, and IOUS identified each of the five tumors that were palpable and five additional tumors that were not palpable (Fig. 1). Intraoperative ultrasonography was significantly better than palpation for operative localization of occult insulinomas (5 of 10 *versus* 10 of 10 localized, p = 0.03). Each of the five tumors found only by IOUS were located in the pancreatic head (Table 1). None of these tumors would have been removed by a blind subtotal pancreatectomy, including the tumor in patient 10 who had previously undergone that procedure elsewhere.

The ultrasound appearance of an insulinoma was typically a discrete sonolucent mass lesion that was well demarcated from the surrounding pancreas (Fig. 1). One insulinoma appeared to have an echogenecity pattern similar to the surrounding pancreas, thus making it difficult to visualize; however that tumor had a clear, sonolucent rim with echogenic borders (Fig. 2). Verification of IOUS findings were confirmed by imaging in two planes and the ability to repeatedly image the same mass lesion.

Both methods of operative localization were positive in five patients. Palpation did not identify any tumors that ultrasound missed. In addition neither palpation nor IOUS had false-positive findings. One insulinoma was not identified by IOUS or palpation and was only identified by pathologic examination following a distal pancreatectomy. This procedure was based on an insulin gradient in the pancreatic tail (patient 7, Table 1, Fig. 3).

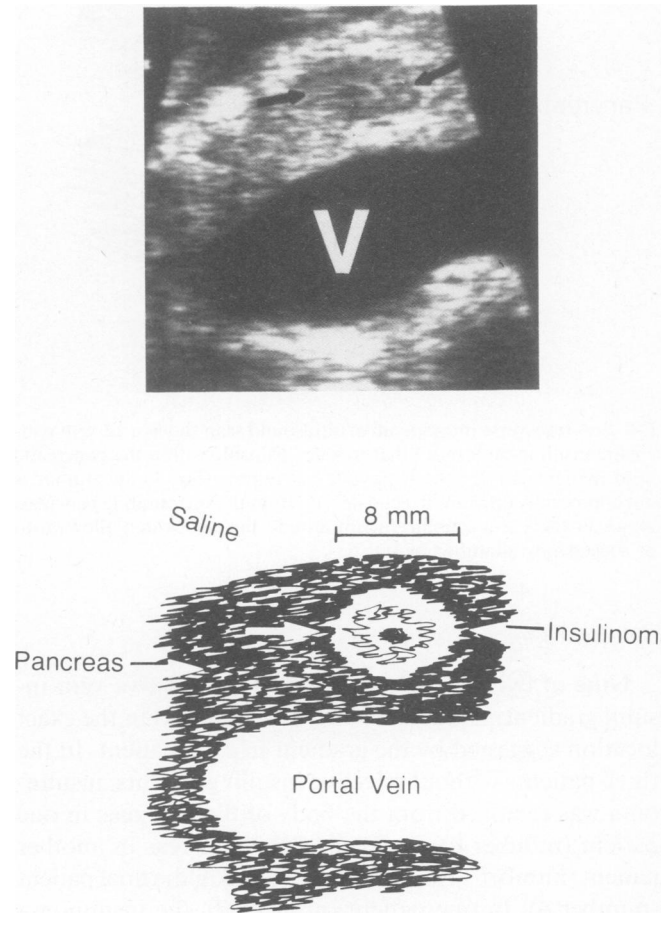

FIG. 1. A transverse IOUS scan shows a small pancreatic insulinoma (arrows) that was not palpable within the pancreatic head (patient 9). The tumor is less echo dense than the surrounding normal pancreas. This tumor measured 8 mm in diameter and was superficial to the portal vein (V) at its origin. The tumor has been dissected partially surgically and one can see saline (sonolucent) around the pancreas near the star.

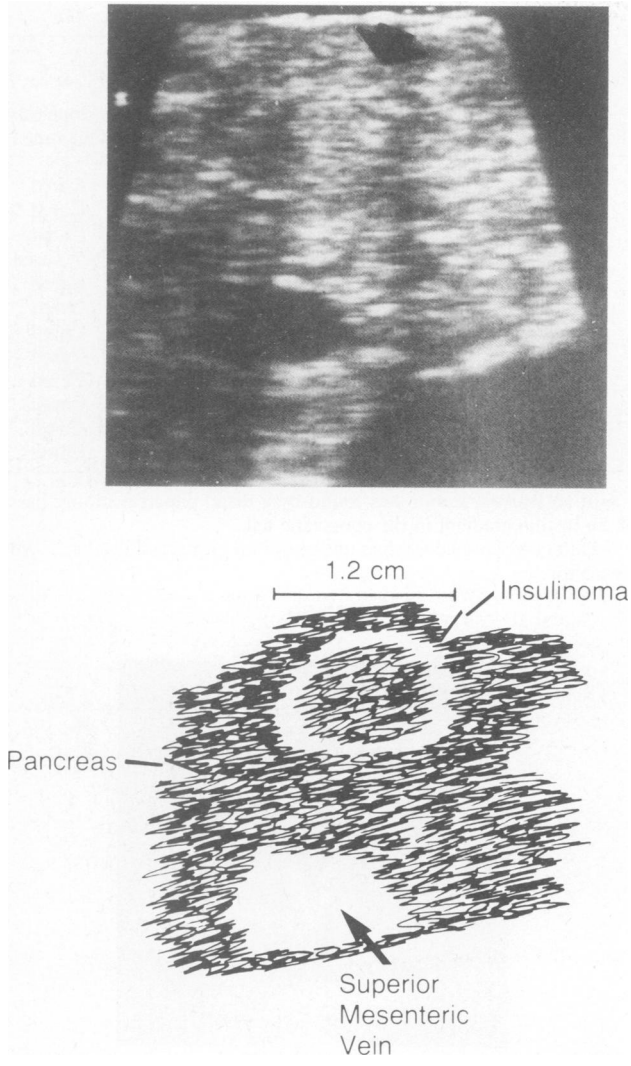

FIG. 2. A transverse intraoperative ultrasound scan shows a 12-mm pancreatic insulinoma (arrow) that was not palpable within the pancreatic head (patient 12). Unlike most islet cell tumors (Fig. 1), this tumor is not appreciably different in echo density from the surrounding pancreas. However there is a sonolucent rim around the tumor that allows it to be successfully identified by IOUS.

Selective Venous Sampling

Nine of twelve patients (75%) had a selective vein insulin gradient, and an insulinoma was found in the exact location suggested by the gradient in each patient. In the three patients without selective insulin gradients, insulinoma was removed from the body of the pancreas in one patient (number 8), the head of the pancreas in another patient (number 11), and was not found in the final patient (number 4). In one patient (number 7), the insulinoma was removed only because of PVS. In this patient PVS demonstrated a marked step-up in the pancreatic tail, but operative maneuvers, including IOUS, did not identify an insulinoma. A distal pancreatectomy was performed based on PVS and a 1-cm insulinoma was removed (Table 1, Fig. 3). In patients with occult insulinoma, PVS correctly predicted the location of the tumor in 9 of 12 patients and correctly predicted that no tumor would be found in another; therefore its results were accurate in 83% of patients, including one patient in whom tumor would not have been removed without it.

Morbidity and Outcome

Venous sampling did not result in complications in any patient. Surgical exploration resulted in significant complications in two patients. One patient required reoperation 2 months after operation for a small bowel obstruction, and another patient required reoperation for a pancreatic abscess. These complications completely resolved. No patient developed diabetes mellitus or exocrine pancreatic insufficiency. The overall complication rate was 17%. There were no therapy-related deaths.

Eleven of twelve patients had a solitary insulinoma removed and each was cured (92% cure rate). The solitary patient who had no insulinoma found has persistent hypoglycemia controlled medically by diazoxide 4 years after unsuccessful surgery.

Discussion

Greater recognition of the symptoms and signs of insulinomas combined with newer assays, including C-peptide and proinsulin levels, have led to an earlier definitive

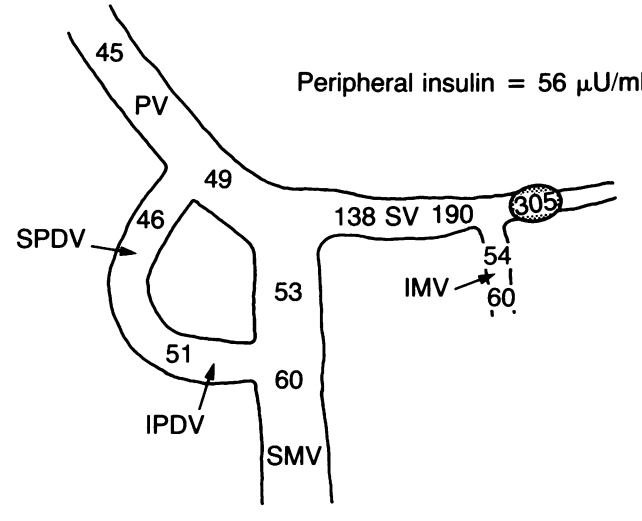

FIG. 3. Transhepatic selective venous sampling of the portal vein and its tributaries for insulin. Venous insulin levels are markedly elevated in the distal splenic vein (shaded circle, patient 7). Intraoperative ultrasound and palpation of the pancreas body and tail did not reveal an insulinoma. A distal pancreatectomy was performed based on the PVS gradient and the pathologists confirmed the presence of a 1-cm insulinoma. SPDV, superior pancreaticoduodenal vein; IPDV, inferior pancreaticoduodenal vein; PV, portal vein; SV, splenic vein; SMV, superior mesenteric vein; and IMV, inferior mesenteric vein. Insulin concentrations are given in μU/mL.

diagnosis of insulinoma.[3,4,20] Early diagnosis may have contributed to another problem in the management of these patients, inability to localize the tumor before operation. Despite the fact that many patients with insulinomas will have tumors localized by angiography,[11,12] the incidence of patients with occult insulinomas seen at the National Institutes of Health, as reported elsewhere,[13] has increased from 3 of 19 patients (16%), as reported previously[11] to 12 of 23 patients (52%), as presently reported. The management of these patients remains a difficult clinical problem.

Occult insulinomas generally are small, making localization both before and during operation difficult. If tumors are not found at exploration, surgeons have recommended blind pancreatic resection to remove the tumor along with normal pancreas.[5-7] The pancreas and spleen are removed from left to right such that more and more normal pancreas is resected. Some have recommended intraoperative monitoring of blood glucose to demonstrate a rebound hyperglycemia after removal of the pancreas with the insulinoma to document that the insulinoma has been removed.[7] Blind resections in this manner are morbid and have a 33% chance of not removing the insulinoma because some occult insulinomas will be in the pancreatic head. In fact, in the present series, 5 of 11 occult tumors (45%) were located in the pancreatic head and would have been unsuccessfully treated by blind subtotal pancreatectomy. We believe that the results of this current study indicate that blind pancreatectomy is not a reasonable strategy for patients with occult insulinoma.

Two newer localization techniques (PVS and IOUS) have changed the operative management of patients with occult insulinoma. Portal venous sampling for insulin can pinpoint reliably the exact region of the pancreas with the insulinoma in most patients. In this series it identified the region in 75% of patients. There were no false-positive results (Table 1, Fig. 3). Precise regional localization allows meticulously focused dissection of a pancreatic region and purposeful, accurate probing of a smaller area with IOUS. In the nine patients with positive regional localization by PVS, operative ultrasound localized the tumor in eight while palpation identified the tumor in only 4 patients (Table 1). Portal venous sampling identified the region on which the surgeon could focus IOUS. In the final patient with positive PVS (number 7), despite negative operative maneuvers, including IOUS to localize the insulinoma, an enlightened resection based on PVS information could be performed and was successful (Fig. 3). In addition, although PVS is an invasive procedure with needles, catheters, and guide wires traversing the liver, it has minimal morbidity. In our experience no patients with occult insulinoma had complications from PVS; and in the gastrinoma context, only 4 of 27 patients (15%) had prolonged pain after the procedure that resolved slowly on its own without treatment.[22] Portal venous sampling increases cost and requires considerable expertise by the radiologist, but if an insulin gradient is obtained, it reliably localizes the exact pancreatic region with the insulinoma. If there is no insulin gradient on PVS, surgery is still indicated because most patients (two of three) will have successful operations (Table 1).

The major breakthrough in the localization of occult insulinomas is the use of intraoperative ultrasound. It is a procedure performed jointly by the surgeon and ultrasonographer that requires each person for best results. Because insulinomas are almost always within the pancreas and the ultrasound appearance of the tumor is so different from the pancreas (Fig. 1), small, occult insulinomas can be visualized reliably by IOUS. Intraoperative ultrasonography localized significantly more occult insulinomas than palpation. It allowed the successful enucleation of five pancreatic head insulinomas that would not have been able to be removed by another surgical procedure except a morbid Whipple pancreaticoduodenectomy. Intraoperative ultrasonography was necessary to facilitate excision of these insulinomas. An incision was planned based on ultrasound determination of the shortest, most direct route to the tumor without traversing the pancreatic duct or other vital structures. After the incision was made, IOUS was performed again as the pancreas was traversed. The shortest path was continually reconfirmed by IOUS until the tumor was visualized and then an enucleation could be performed. The ability of IOUS to find insulinomas that are not palpable also has been reported by others,[24] further corroborating the utility of this instrument to operatively localize occult tumors. Therefore the advantages of the use of operative ultrasound in the treatment of insulinomas include (1) precise operative localization, (2) enucleation of nonpalpable nonvisible tumors, and (3) avoidance of ductal injuries as well as injuries to other vital structures by precise localization of adjacent vital structures such as the portal vein (Fig. 1).

The results of the present study support the strategy of portal venous sampling for insulin to localize a specific region with the insulinoma and surgery guided by IOUS to identify and remove the tumor in patients with occult insulinomas. In 12 patients managed with this strategy, small insulinomas were removed in 11 patients and each was cured (92%). This high degree of success was achieved with acceptable morbidity. Some may suggest that PVS is not absolutely necessary because it was only positive in 75% of patients and two of three patients in whom it was negative still had successful operations. We argue that it is helpful because one patient (number 7 Table 1, Fig. 3) had a successful operation primarily because of PVS. It produced no false-positive results, so one can confidently

plan a pancreatic resection procedure based on an insulin gradient if no tumor is identified during exploration. The use of intraoperative ultrasound markedly improved the results because it identified significantly more insulinomas than palpation and it guided their successful enucleation.

We conclude that IOUS greatly facilitates the excision of occult insulinomas. Exploratory surgery for occult insulinomas should not be performed without the use of IOUS. The exploration for occult insulinomas should no longer rely on blind distal or subtotal pancreatectomy,[5-8] but rather on precise localization of the tumor facilitated by preoperative PVS and IOUS. Because of the high overall success rate demonstrated here, pure medical management of hypoglycemia in patients with occult insulinoma should be reserved only for the few patients (8%) in whom this strategy is unsuccessful.

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